CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Triflusulfuron-methyl

Chemical Code # 3875, **Tolerance #** 51974
SB 950 # NA

11/18/05

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap; possible adverse effect
Chronic toxicity, dog:	No data gap; no adverse effect indicated
Oncogenicity, rat:	No data gap; no adverse effect indicated
Oncogenicity, mouse:	No data gap; no adverse effect indicated
Reproduction, rat:	No data gap; no adverse effect indicated
Teratology, rat:	No data gap; no adverse effect indicated
Teratology, rabbit:	No data gap; no adverse effect indicated
Gene mutation:	No data gap; no adverse effect indicated
Chromosome effects:	No data gap; possible adverse effect
DNA damage:	No data gap; no adverse effect indicated
Neurotoxicity:	No data gap; no adverse effect indicated

Toxicology one-liners are attached.

All record numbers through 147905 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T051118
Revised by T. Moore, 11/18/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 51974-058; 127247**; "Combined Chronic Toxicity/Oncogenicity Study with DPX-66037-24 Two-Year Feeding Study in Rats" (Author: L.B. Biegel; E.I. du Pont de Nemours & Company, Inc., Newark, DE; Project No. HLR 3-93; 5/6/93); DPX-66037-24 (95.6% triflusulfuron-methyl); 0, 10, 100, 750, 1,500 ppm (averaged intake (M) 0, 0.406, 4.49, 30.6, 64.5 and (F) 0, 0.546, 5.47, 41.5, 87.7 mg/kg/day, respectively)in diets; 62 rats/sex/dose; observations- statistically significant decreased body weights and body weight gains of rats in the 1,500 ppm group; in females fed 750 and 1500 ppm a decreased incidence of mammary masses was noted when compared to controls, in the highest dosed females statistically significant increases of sciatic nerve myelin/axon degeneration occurred, the 1500 ppm males had no increased incidence of this lesion but showed increased lesion severity; males in 750 and 1500 ppm groups had decreased erythrocyte counts and mean serum triglyceride concentrations; high dosed males showed decreased serum calcium concentrations, an increase in the absolute and relative testes weight and statistically significant increases of both Leydig cell hyperplasia and adenomas; **NOEL(M)**= 100 ppm (based on decreased erythrocyte counts, decreased body weights, decreased body weight gain, increased severity of sciatic nerve lesions, Leydig cell hyperplasia and Leydig cell adenomas); **NOEL(F)**= 750 ppm (based on decreased body weight and increased incidence of sciatic nerve degeneration); **Possible Adverse Effect:** Leydig cell hyperplasia and adenomas; **Acceptable**. (Miller, 12/13/93)

51974-059; 127248; "Mechanisms of Rat Leydig Cell Tumor Induction by DPX-66037-24" (Author: L.B. Biegel; E.I. du Pont de Nemours & Company, Inc., Newark, DE; Project No. HLR 575-93; 10/11/93); DPX-66037-24 (95.6% triflusulfuron-methyl); 0, 1000, 1500, 2000 ppm administered by gavage; 10 male rats/dose; statistically significant decreases in absolute and relative accessory sex glands (prostate, seminal vesicles and coagulating glands) weights were observed in all dose groups, serum estradiol levels were statistically decreased; hCG-challenged rats (10 control, 10 at 2000 ppm) showed statistically significant elevated serum testosterone levels and decreased serum estradiol levels with no statistically different serum LH, FSH, prolactin, or interstitial testosterone and estradiol levels, **no adverse effects indicated; Supplemental.** (Miller, 12/15/93)

51974-059; 127248; "Mechanisms of Rat Leydig Cell Tumor Induction by DPX-66037-24" (Author: L.B. Biegel; E.I. du Pont de Nemours & Company, Inc., Newark, DE; Project No. HLR 575-93; 10/11/93); DPX-66037-24 (95.6% triflusulfuron-methyl); tested in rat Leydig cells with and without hCG, 3 wells per concentration, test concentration dissolved in DMSO and added to the media at final concentrations of 0, 0.1, 0.5, 1, 10, 100 and 1000 uM; 5 hours total exposure to DPX-66037-24, media was collected and frozen until analyzed by radioimmunoassay for steroid concentration (testosterone, estradiol, and progesterone); a statistically significant increasing trend in testosterone production of cells with no hCG-stimulation, and testosterone production of cells incubated with 1000 uM of DPX-66037-24 was elevated and statistically significant, hCG and non-hCG treated cells incubated with 100 and 1000 uM DPX-66037-24 had decreased estradiol; data suggests that DPX-66037 acts as an aromatase inhibitor, **no adverse effects indicated**; **Supplemental.** (Miller, 12/16/93)

51974-059; 127248; "Mechanisms of Rat Leydig Cell Tumor Induction by DPX-66037-24" (Author: L.B. Biegel; E.I. du Pont de Nemours & Company, Inc., Newark, DE; Project No. HLR 575-93; 10/11/93); DPX-66037-24 (95.6% triflusulfuron-methyl); hormone levels in serum collected from rats utilized in the DPX-66037-24 chronic toxicity/oncogenicity study was measured, a statistically significant increasing trend of testosterone and FSH levels was noted with individual increases not statistically different from controls except FSH levels of the 1,500 ppm group; a statistically significant trend of decreasing estradiol levels was noted with individual decreases not statistically

different from controls; there were no statistically significant effects on serum prolactin or LH levels although LH levels of the 1,500 ppm group was slightly elevated; **no adverse effects indicated**; **Supplemental.** (Miller, 12/20/93)

51974-059; 127248; "Mechanisms of Rat Leydig Cell Tumor Induction by DPX-66037-24" (Author: L.B. Biegel; E.I. du Pont de Nemours & Company, Inc., Newark, DE; Project No. HLR 575-93; 10/11/93); DPX-66037-24 (95.6% triflusulfuron-methyl); In vitro hepatic microsomal aromatase activity was determined using hepatic microsomes from ammonium perfluorooctanoate (C8) induced male rats with androstan-4-ene-3,17-dione[1beta-3H] as the substrate in the presence of 0, 0.01, 0.02, 0.05, 0.1, 0.2, or 0.5 uM DPX-66037-24; DPX-66037-24 inhibited C8 induced aromatase activity in a dose dependant manner; **no adverse effects indicated**; **Supplemental.** (Miller, 12/21/93)

51974-059; 127248; "Mechanisms of Rat Leydig Cell Tumor Induction by DPX-66037-24" (Author: L.B. Biegel; E.I. du Pont de Nemours & Company, Inc., Newark, DE; Project No. HLR 575-93; 10/11/93); DPX-66037-24 (95.6% triflusulfuron-methyl); A cytochrome P-450 spectral binding assay was performed using hepatic microsomes from phenobarbital-induced rats and DPX-66037-24 as the ligand, DPX-66037-24 produced a type II binding spectra with a peak at 435 nm and a trough at 415 nm indicating inhibition of cytochrome P-450 isozymes; **no adverse effects indicated**; **Supplemental.** (Miller, 12/20/93)

Supplemental Studies Conclusions

DPX-66037-24 appears to act as an aromatase inhibitor causing a reduction in serum estradiol levels. Sustained reduction of estradiol disrupts the negative feedback control of LH and FSH resulting in elevated levels of serum LH and FSH. These elevated levels of LH and FSH are ultimately responsible for the observed increases in Leydig cell hyperplasia and adenoma formation. The author indicates that there are numerous studies that indicate that rats are more susceptible than humans to chemically-induced, hormonally-mediated Leydig cell tumor formation.

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

** 51974-066; 138127; "A Chronic (1 year) Oral Toxicity Study in the Dog with DPX-66037-24 via the Diet" (Author: C.S. Auletta, Pharmaco LSR Inc., East Millstone, NJ; 4/28/93); DPX-66037-24 (Lot # 2, 95.6% purity); 0, 35, 875, 3500 ppm/day via dietary admixture; 5 dogs/sex/dose; observations-two high dose animals were sacrificed in moribund condition; high dose dogs showed a slight anemia that was most pronounced at month 3; increased mean serum alkaline phosphatase values were seen in high dose males throughout the study; high dose animals also showed elevated liver weights consistent with microscopic observations of minimal centrilobular hepatocellular hypertrophy seen in both males and females; no other treatment related effects were noted in any other parameter; **no adverse effects**; **NOEL(M/F**)= 875 ppm (based on clinical pathology alterations, possible test substance related mortalities, increased liver weights, and microscopic liver pathology); **Acceptable** (Miller, 9/15/95)

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

** 51974-061; 127768; "Oncogenicity Study with DPX-66037-24 Eighteen-Month Feeding Study in Mice" (Author: L.A.Biegel; E.I. du Pont de Nemours & Company, Newark, DE; Project No. HLR 529-92; 4/1/93); DPX-66037-24 (95.6% triflusulfuron-methyl); 0, 10, 150, 2,500, 7,000 ppm (averaged intake (M) 0, 1.37, 20.9, 349, 1,024 and (F) 0, 1.86, 27.7, 488, 1,360 mg/kg/day, respectively)in diets; 110 rats/sex/dose; observations-decreased body weight gain in both sexes

at 7000 ppm level but only statistically significant in females, increased absolute and relative liver weights noted but not statistically significant in both sexes in the 2,500 and 7,000 ppm groups, statistically significant elevations of hepatic cytochrome P-450 was observed in both sexes in the 7,000 ppm group at 2 week sampling and in females at 3 months, an increase in hepatic foci of cellular alteration incidence in both sexes of the 2,500 and 7,000 ppm groups was statistically significant for females, an increased incidence of intrahepatocellular erythrocytes in 2,500 ppm males and 7,000 ppm females, statistically significant increased incidence of adenomas and carcinomas occurred in males of the 7,000 ppm group was within the historical control level for this mouse strain at this laboratory; **no adverse effects**; NOEL(M/F)= 150 ppm (based on decreased body and organ weights, microscopic findings and decreased hepatic cytochrome P-450 activity); **Acceptable**. (Miller, 1/27/94)

REPRODUCTION, RAT

** 51974-057; 126843; "Reproductive and Fertility Effects with DPX-66037-24 Multigeneration Reproduction Study in Rats" (Author: M. E. Hurtt; E.I. du Pont de Nemours & Company, Inc., Newark, DE, Project No. HLR 231-92, 4/20/93); DPX-66037-24 (95.6% Triflusulfuron-methyl); 0, 10, 100, 750, 1,500 ppm dietary; 30 Crl: CD BR rats/dose both P1 and F1; observations- no dose related mortalities were observed, statistically significant lower body weights and body weight gains were observed in P1 (two highest doses) and F1 (1500 ppm) males, body weight effects were accompanied by statistically significant decreases in food consumption (1500 ppm group), in female P1 rats statistically significant lower mean body weight gains were noted (750, 1500 ppm groups) during premating, statistically significant lower mean body weights during gestation and lactation (two highest groups) were also observed, statistically significant decreases in overall food consumption was present in F1 female rats during premating (750, 1500 ppm groups), no additional statistically significant differences were found in other adult parameters; compound related decreases in mean F1 and F2 pup weights (highest two dose groups) were observed but were not statistically significant, there were no significant differences in any other clinical observations in the F1 and F2 pups; generally gross necropsy and histomorphologic findings of adults and offspring were few and were not considered treatment related; **Adult and Developmental NOEL** = 100 ppm of a.i. (based on decreased body weight, body weight gain, food efficiency and decreased pup weights); **Acceptable** (Miller, 11/18/93)

TERATOLOGY, RAT

** 51974-030; 119842; "Teratogenic Study of DPX-66037-24 in Rats" (Author: C.A. Mebus; E.I. du Pont de Nemours & Company, Inc., Newark, DE, Project No. HLR 525-91, 11/1/91); DPX-66037-24 (95.6% Triflusulfuron-methyl); 0, 30, 120, 350, 1000 mg/kg/day oral gavage; 25 Crl: CD BR female rats/dose; observations- maternal effects; five animals died due to dosing injuries; significant decreases in maternal weight changes and feed consumption were observed; fetal effects; significantly increased average number of malformed fetuses were observed, the majority of fetal malformations occurred in one fetus, when individual end points of developmental evaluation criteria were grouped a significant increase was noted in the 350 and 1000 mg/kg dose groups primarily due to retarded renal development and partial ossification of skulls, sternebra or vertebra; no adverse effect; **Maternal NOEL** = 120 mg/kg (based on decreased maternal weight gain and feed consumption), **Developmental NOEL** = 120 mg/kg (based on increased average number of malformed fetuses, retarded fetal development); **Acceptable.** (Miller, 9/27/93)

TERATOLOGY, RABBIT

** 51974-031; 119843; "Teratogenic Study of DPX-66037-24 in Rabbits" (Author: S.M. Murray; E.I. du Pont de Nemours & Company, Inc., Newark, DE, Project No. HLR 575-91, 10/28/91); DPX-66037-24 (95.6% Triflusulfuron-methyl); 0, 15, 90, 270, 800 mg/kg/day oral gavage; 20 Hra:(NZW)SPF female rabbits/dose; observations- maternally toxic at doses of 90 mg/kg and greater, significant increased dose-related mortalities and spontaneous abortions occurred at levels of 270 and 800 mg/kg, during the dosing period the highest two dose groups showed clinical signs of reduced fecal output, reduced fecal size or diarrhea; significant decreases in

maternal weight changes and feed consumption were also observed; histopathological changes were noted primarily in the 800 mg/kg group and included gastric mucosal ulcerations and digestive tract gaseous distension; death losses at 800 mg/kg were extreme and data from remaining dams were markedly different therefore these data were excluded from statistical analysis; no physiological or developmental fetal effects were observed at any dose level; no adverse effect; **Maternal NOEL** = 15 mg/kg (based on animal death, abortions, decreased maternal weight gain and food consumption), **Developmental NOEL** = 800 mg/kg (based on no adverse affects); **Acceptable**. (Miller, 9/24/93)

GENE MUTATION

** 51974-034; 119870; "Mutagenicity Testing of IN 66037-14 in the Salmonella Typhimurium Plate Incorporation Assay" (E.I. du Pont de Nemours and Company, Inc., Newark, DE, Lab. Report No. HLR 238-90, 2/14/91); IN 66037-14, (91.9% purity), tested with Salmonella typhimurium strains TA-1535, TA-97, TA-98 and TA-100 with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); triplicate plates two trials for nonactivated and activated systems; dose range 0-3000 ug/plate; 48 hour incubation; no increase in reversion rate reported; **acceptable**; (Miller, 10/19/93).

** 51974-084 147882; "DPX 66037 Reverse Mutation Assay By The Ames Test"; B. Molinier, Centre International de Toxicologie Miserey - 27005 Evreux, France; Study No. 8721, 7/9/92; Triflusulfuron Methyl Technical (DPX-66037-59, 98.6% purity), tested with Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98 and TA-100 with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); triplicate plates, two independent assays for nonactivated and activated systems; dose range 0-1000 ug/plate; 48 to 72 hours incubation; no increase in reversion rate reported; **Acceptable**; (Miller, 10/15/96).

** 51974-035; 119874; "Mutagenicity Evaluation of DPX 66037-24 in the CHO/HPRT Assay" (E.I. du Pont de Nemours and Company, Newark, DE, Lab. Report No. HLR 656-91, 11/13/91); DPX 66037-24, (95.6% purity), tested in Chinese hamster ovary cells with and without activation by Aroclor 1254 induced rat liver S9 fraction; triplicate plates two trials for nonactivated and activated systems; dose range 0-2000 ug/ml; 48 hour incubation; due to severe toxicity at 2000 ug/ml insufficient cells were available to evaluate mutations at that concentration; no increase in reversion rates were reported; **Acceptable**; (Miller, 10/21/93).

CHROMOSOME EFFECTS

** 51974-037; 119876; "Mouse Bone Marrow Micronucleus Assay of DPX-66037-24" (E.I. du Pont de Nemours and Company, Newark, DE, Lab. Report No. HLR 666-91, 12/20/91); DPX 66037-24 (95.6% purity); Crl:CD-1(ICR)BR mice; 5-6 mice/sex/dose; doses 0, 1250, 2500, and 5000 mg/ml; cyclophosphamide 40 mg/kg positive control; bone marrow samples taken at 24, 48, and 72 hours after dosing and 24 hours after dosing for the positive control; no statistically significant increases in micronucleus frequency were observed at any dose level; statistically significant depressions in the PCE:NCE ratios among the 5000 mg/kg dosage mice were observed at the 48 hour sampling time; three mice (1M,2F) died in the 5000 mg/kg group; within approximately 3-4 hours after dosing the majority of animals at all dose levels showed lethargy and/or abnormal gaits with symptoms clearing by 48 hours. **no adverse effects**, **Acceptable**; (Miller, 10/26/93).

** 51974-086 147884; "DPX 66037 Micronucleus Test by Oral Route in Mice"; B. Molinier, Centre International de Toxicologie Miserey - 27005 Evreux, France, 9/14/92; Triflusulfuron Methyl Technical (DPX-66037-59, 98.6% purity), tested in mouse bone marrow erythrocytes; Swiss OF1 mice; 5 mice/sex/group; single 5000 mg/kg dose; bone marrow samples taken at sacrifice times of 24 and 48 hrs in treated and vehicle groups and at 24 hrs for positive control dose groups, 2000 polychromatic erythrocytes/animal were scored for micronuclei; positive control functional; test article did not produce an increase in induced micronuclei in mice bone marrow erythrocytes; **no adverse effects; Acceptable** (Miller, 10/8/96)

**** 51974-094 147900**; "In Vitro Evaluation of H-19439 (DPX-66037-59) For Chromosome Aberrations in Human Lymphocytes"; K. S. Bentley, E.I. du Pont de Nemours and Company, Inc., Newark, DE, Lab. Report No. HLR 416-92, 8/12/92; H-19439 (Triflusulfuron Methyl, DPX-66037-59, 98.7% purity), tested with In vitro treatments of human lymphocytes for clastogenic activity with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); two trials for nonactivated and activated systems each with replicate cultures; 100 cells (50 from each replicate)/concentration/trial were scored for structural chromosomal aberrations; dose range 0-2.0 mg/culture; test material exposure: 3 hrs followed by post-treatment incubation of 19-20 hrs (trial 1) or 43 hrs (trial 2); Possible Adverse Effect: in both trials with activation, a statistically significant and reproducible increase in the number of aberrant cells was noted at 2.0 mg/ml. **Under conditions of this assay, H-19439 is positive**. **Acceptable**; (Miller, 10/2/96).

** 51974-085 147883; "DPX 66037 In Vitro Mammalian Cytogenetic Test in Human Lymphocytes"; B. Molinier, Centre International de Toxicologie Miserey - 27005 Evreux, France, Study No. 8722, 9/14/92; Triflusulfuron Methyl (DPX-66037-59), (98.6% purity), tested with In vitro treatments of human lymphocytes for clastogenic activity with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); two trials for nonactivated and activated systems each with duplicate cultures; 200 metaphase cells/concentration/trial were scored for mitotic index and structural chromosome abberations; dose range: (trial 1) 0, 12.5, 25, 50, 100, 200, 400 ug/ml; (trial 2, w/out activation) 0, 50, 100, 200 ug/ml, (trial 2, with activation) 0, 100, 200, 400 ug/ml; test material exposure: 2 hr with S9 activation followed by 22 hr (trial 1) or 22 and 46 (trial 2) hr incubation, 24 and 48 hr without S9 activation in trials 1 & 2, respectively. In both trials the incident of aberrant cells (clastogenic activity) in treated cultures was similar to that of control cultures values for the two independent tests and for both sampling times. **Acceptable**; (Miller, 10/16/96).

**** 51974-098 147905**; "In Vitro Evaluation of DPX-66037-24 For Chromosome Aberrations in Human Lymphocytes"; K. S. Bentley, E.I. du Pont de Nemours and Company, Inc. Newark, DE, Study Report No. 775-91, 12/5/91; Triflusulfuron Methyl (DPX-66037-24), (95.6% purity), tested with In vitro treatments of human lymphocytes for clastogenic activity with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); 3 trials for activated systems, 2 trials for nonactivated systems; dose range: (trial 1) 0.1, 0.5, 1.0, 1.5, 2.0 mg/ml; (trial 2) 0.1, 1.0, 1.5, 2.0 mg/ml, (trial 3) 1.5, 1.7, 1.85, 2.0 mg/ml; 3 hrs treatment incubations. Cytotoxicity was present at 2.0 mg/ml with activation in all trials as indicated by mitotic index depression. The second trial with activation showed increased chromosome aberrations at 2 mg/ml. In the third activated trial statistically significant increases in aberrations were noted at 1.7, 1.85, and 2.0 mg/ml. Therefore, the test article is positive for clastogenicity in this assay. **Possible Adverse Effects; acceptable**; (Miller, 10/17/96).

DNA DAMAGE

** 51974-036; 119875; "Assessment of DPX-66037-24 in the In Vitro Unscheduled DNA Syntheses Assay in Primary Rat Hepatocytes" (E.I. du Pont de Nemours and Company, Newark, DE, Lab. Report No. HLR 675-91, 11/7/91); DPX 66037-24, (95.6% purity), tested in Crl:CD BR male rat hepatocyte cultures; 1 rat/trial; dose range 0-2000 ug/ml; cells labelled in vitro with [methyl-3H] thymidine in an 18 hour incubation; UDS by autoradiography; 25 cells from each culture, two cultures from each concentration, were scored individually; cytotoxicity was determined by measuring lactate dehydrogenase activity; visual examination determined cytotoxicity was present at 1500 and 2000 ug/ml; no UDS was observed at any concentration; **Acceptable**; (Miller, 10/21/93).

SUPPLEMENTAL GENOTOXICITY STUDIES

51974-095 147902; "Mutagenicity Testing of IN D8526-2 in the Salmonella Typhimurium Plate Incorporation Assay"; V.L. Reynolds, E.I. du Pont de Nemours and Company, Inc., Newark, DE,

Lab. Report No. HLR 731-91, 8/24/92; IN D8526-2, (98.4% purity), tested with Salmonella typhimurium strains TA-1535, TA-97, TA-98 and TA-100 with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); triplicate plates, two trials for nonactivated and activated systems; dose range 0-5000 ug/plate; 48 hour incubation; no increase in reversion rate reported; **Supplemental**; (Miller, 10/2/96).

51974-096 147903; "Mutagenicity Testing of IN E7710-3 in the Salmonella Typhimurium Plate Incorporation Assay"; V.L. Reynolds, E.I. du Pont de Nemours and Company, Inc., Newark, DE, Lab. Report No. HLR 734-91, 8/24/92; IN E7710-3, (98.7% purity), tested with Salmonella typhimurium strains TA-1535, TA-97, TA-98 and TA-100 with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); triplicate plates two trials for nonactivated and activated systems; dose range 0-5000 ug/plate; 48 hour incubation; no increase in reversion rate reported; **Supplemental**; (Miller, 10/2/96).

51974-97 147904; "Mutagenicity Testing of IN M7222-3 in the Salmonella Typhimurium Plate Incorporation Assay"; V.L. Reynolds, E.I. du Pont de Nemours and Company, Inc., Newark, DE, Lab. Report No. HLR 741-91, 8/24/92; M7222-3, (99.9% purity), tested with Salmonella typhimurium strains TA-1535, TA-97, TA-98 and TA-100 with and without activation by Aroclor 1254 induced rat liver homogenate activation system (S-9 mix); triplicate plates, two trials for nonactivated and activated systems; dose range 0-5000 ug/plate; 48 hour incubation; no increase in reversion rate reported; **Supplemental**; (Miller, 10/1/96).

NEUROTOXICITY

Acute Neurotoxicity, Rat

51974-083; 147880; "Acute Neurotoxicity Study of DPX-66037-24 (Triflusulfuron methyl) Administered Orally via Gavage to Crl:CDBR VAF/Plus Rats" J.A. Foss; E.I. du Pont de Nemours & Company, Newark, DE; Project No. DuPont HLO 126-93; 9/29/94; DPX-66037-24 (95.6% Triflusulfuron-methyl); doses 0, 500, 1000, 2000 mg/kg/day by gavage for 15 days, 2 replicates; 10 rats/sex/dose; observations-No specific evidence of behavioral or histological neurotoxicity at any dose level. The 1000 and 2000 mg/kg dosages reduced feed consumption values in male rats on days 1 and 2. The highest concentration reduced body weight gains in male rats on days 1 to 2 and 1 to 15 of the study. Female rats were unaffected in any parameter at all dose levels. NOEL(F)= 2000 mg/kg (based on no effects); NOEL(M)= 500 mg/kg (based on decreased body weight gain and reduced consumption); **No adverse effects; **Acceptable**. (Miller, 10/18/96)

Subchronic Neurotoxicity, Rat

51974-099; 147828; "Subchronic Neurotoxicity Study of DPX-66037-24 (Triflusulfuron methyl) Administered Orally via the Diet to Crl:CDBR VAF/Plus Rats" J.A. Foss; E.I. du Pont de Nemours & Company, Newark, DE; Project No. DuPont HLO 127-93; 9/29/94; DPX-66037-24 (95.6%, Triflusulfuron-methyl); male doses (consumed mean doses [mg/kg/day] range) 0, 100 (4.4-9.7), 750 (72.1-32.8), 1500 (143.1-66.5), 3000 (272.1-133.8) ppm in diets, female doses (consumed mean doses [mg/kg/day] range) 0, 100 (5.5-9.7), 750 (67.7-40.0), 1500 (136.2-79.0), 3000 (258.3-163.4) ppm in diets ; 11 rats/sex/dose; observations-No specific evidence of behavioral or histological neurotoxicity at any level. The 750 ppm and higher dietary concentrations significantly reduced body weight gains and feed consumption values and the two highest concentrations significantly reduced the average body weights in females. The 3000 ppm concentration significantly reduced body weight gains and showed a trend to reduce average body weights and feed consumption values in male rats. NOEL(F)= 100 ppm (based on decreased body weight gain); NOEL(M)= 1500 ppm (based on decreased body weight gain); **No adverse effects; **Acceptable**. (Miller, 10/17/96)

METABOLISM

51974-0101; 147832; "The Metabolism of ^{14}C-DPX-66037 in Rats"; (D.R. Hawkins, *et. al.*; Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. HRC/DPT 224/911279; 1/17/92); Sprague-Dawley rats of both sexes were dosed orally by gavage with either (1) triazine [U-^{14}C]DPX-66037 (lot no. 2622-175, specific activity: 79.5 uCi/mg, radiochemical purity: 95 to 97%) or (2) [ester carbonyl-^{14}C]DPX-66037 (lot no. 2587-258, specific activity: 82.6 uCi/mg, radiochemical purity: 97 to 98%). The specific activity of the dosing preparations were adjusted with the addition of non-radiolabeled DPX-66037 technical (Du Pont no. IN-66037-13, purity: 91.2%).. Four Groups were included in the study. In Group A, 5 animals/sex received a single treatment of 25 mg/kg of radiolabeled test material No. 1. In Group B, 5 animals/sex received 14 treatments of 25 mg/kg/day of unlabeled test material and then a single dose of 25 mg/kg of radiolabeled test material No. 1. In Group C, 5 animals/sex received a dose of 250 mg/kg of radiolabel test material No. 1. In Group D, 5 animals/sex received a single dose of 250 mg/kg of radiolabeled test material No. 2. Urine and fecal samples were collected at various time points up to 5 days postdose or post final dose (Group B). At 5 days post-dose, the animals were euthanized and selected tissues were analyzed for radiolabeled compound. The females demonstrated a higher percentage of radiolabel recovery in the urine than did the males for all of the treatment groups (Group A: 61 vs. 77 5, Group B: 58 vs. 70%, Group C: 37 vs. 57%, Group D: 30 vs. 51%). The percentage of administered dose which was recovered in the feces of the males ranged from 35 to 41% for the 25 mg/kg treatment groups and from 63 to 72% for the 250 mg/kg groups. For the females, the range of recovery in the feces for the 25 mg/kg treatment groups was 21 to 28% and for the 250 mg/kg treatment groups, 43 to 46%. For Groups A and B, 46 to 58% of the total dose was recovered within the first 24 hours. For the 250 mg/kg treatment groups, the 24 hour recovery ranged from 54 to 76% of the total dose. Pretreatment or the

positioning of the radiolabel did not affect the excretion profile. At 120 hours post-dose, the liver was the primary site of recovery in the tissues with a 2 to 5 times greater concentration of radiolabel than that found in the plasma. The metabolic profile revealed the recovery of DPX-66037 at levels of 1 to 2% and 19 to 34% of administered dose in the 25 mg/kg and 250 mg/kg treatment groups, respectively. The primary biotransformation pathway was demethylation of the dimethylamino substituent on the triazine ring. Cleavage of the sulfonylurea bridge resulted in the formation of the methyl saccharin (W6725), N-desmethyl triazine amine (E7710), and N,N-bis-desmethyl triazine amine (M7222). **Study unacceptable**, not upgradeable (no assessment of the test material's absorption was performed). (Moore, 11/15/05)

51974-064; 129613; "Metabolism of DPX-66037 in the Goat-Attachment 1: The Metabolism of 14C-DPX-66037 in the Goat Following Administration at a Level Equivalent to 10 ppm in the Diet", D.R. Hawkins et. al.; Huntington Research Centre Ltd., Cambridgeshire, England, Document # AMR-1640-90; [Triazine-U-14C]DPX-66037 (Lot# 2622-175, 95.9% purity, S.A.= 79.5 uCi/mg); [Ester carbonyl-14C]DPX-66037 (Lot# 2587-258, 96.5% purity, S.A. = 82.6 uCi/mg); 1 (F) goat/dose; dose frequency and level- 15 mg/day of either ester carbonyl-14C or Triazine-14C DPX-66037, once daily for five days; observations- By time of sacrifice 98.4% of the total ester carbonyl-14C dose was recovered in urine (80.7%) with liver and kidneys retaining 1.0% and 0.2%, respectively; and 0.5% transferred to milk; 78.9% of the total triazine-14C dose was recovered mainly in urine (57.0%) and feces (19.2%) with liver and kidneys retaining 0.2% and 0.03% dose, respectively; and 0.2% transferred to milk; approximately 14% of either dose was excreted unchanged in urine; metabolites being formed by N-demethylation of the dimethylamino group attached to the triazine ring and by hydrolysis of the sulphonylurea linkage, intermediate N-hydroxylmethyl metabolites were also detected in urine; **No adverse effects**; **Supplemental.** (Miller, 9/14/95)

51974-064; 129613; "Metabolism of DPX-66037 in the Goat-Attachment 2: The Distribution and Excretion of Radioactivity Following Administration of Metabolism of 14C-DPX-66037 to Goats at a Level of 0.2 ppm", D.R. Hawkins et. al.; Huntington Research Centre Ltd., Cambridgeshire, England, Document # AMR-2191-91; [Triazine-U- 14C]DPX-66037 (Lot# 2622-175, 95.9% purity, S.A.= 79.5 uCi/mg); [Ester carbonyl-14C]DPX-66037 (Lot# 2587-258, 96.9% purity, S.A.= 82.6 uCi/mg); 1 (F) goat/dose; dose frequency and level- 0.3 mg/day/goat once daily of each form for five days, 1 control goat placebo dosed for five days; observations- By time of sacrifice 88.6% of the total ester carbonyl-14C dose was recovered in urine (72.9%) with liver and kidneys retaining 0.5% and 0.1%; respectively, and 0.1% transferred to milk; 79.4% of the total triazine-14C dose was recovered in urine (57.5%) and feces (18.3%) with liver and kidneys retaining 0.8% and 0.1%; respectively, and 0.4% transferred to milk; the N-demethylated analogue of DPX-66037 was the major urinary metabolite (13-14%) in both radiolabled dosed goats, the major metabolite formed from the ester carbonyl 14C dose material was methyl saccharin (34% in urine) formed by hydrolysis of the sulphonylurea linkage, the intermediate N-hydroxylmethyl metabolite represented 3-4% of the total dose; **No adverse effects**; **Supplemental.** (Miller, 9/14/95)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Studies

51974-028; 119833; "Subchronic Oral Toxicity: 90-Day Study with DPX-66037 Feeding Study in Rats" (Author: C.A. Mebus, E.I. du Pont de Nemours & Company, Inc., Newark, DE, Project No. 523-90, 1/9/91); DPX-66037(95.8% triflusulfuron-methyl); 0, 100, 2000, 10,000, 15,000 ppm (M: 6.20, 127, 646, 965 and F: 7.54, 150, 774, 1070 mg/kg equivalency) in diets; 10 Crl: CDBR rats/sex/dose; no mortalities were observed, significantly decreased mean body weights and body weight gains in both sexes at three highest doses, decreased food consumption in male rats fed 10,000 and 15,000 ppm and females highest three doses; sporadic increased and decreased absolute and relative organ weights were observed with significantly increased relative liver weights noted in three highest dosed females and males at 15,000 ppm levels; highest dosed males had decreased mean absolute testicular weights; hematological findings indicate a mild hemolytic anemia at the three highest doses, decreased serum glucose and phosphate noted in both sexes in two highest treatment groups, urine volume and pH was decreased in males in the

10,000 and 15,000 ppm groups; histologic effects included testicular atrophy/degeneration, oligospermia (15,000 ppm), renal tubular epithelial cell degeneration (1 male, 9 females 15,000 ppm) and renal hemosiderosis (males and females three highest doses); at these relatively high oral doses some of these symptoms and pathology are not unexpected most likely attributable to inanition; NOEL(M/F)= 100 ppm (based on decreased body weights, decreased body weight gains, decreased food efficiency, increased mean relative liver weights and regenerative anemia); **Acceptable.** (Miller, 9/14/93)

51974-092; 147895; Subchronic Oral Toxicity; 821; Rat; "90-Day Study with DPX-66037-59 Feeding Study in Rats"; L.A. Biegel; E.I. du Pont de Nemours an Co., Haskell Lab. for Tox. and Indust. Medicine, Newark, DE; Lab. Report No. HRL 528-92; 10/30/93; Triflusulfuron Methyl (DPX-66037-59, 98.7% purity); 0, 100, 2000, 10000, 15000 ppm (M: 0; 6.56; 133; 658; 1036 and F: 0; 7.71; 153; 783; 1124 mg/kg equivalency) in diets; 10 Crl:CDBR rats/sex/dose: No test article related mortalities. Statistically significant decreases in body weight and body weight gain (M & F: 10000, 15000). Slight decreases in mean final body weight and body weight gain was also observed in the 2000 ppm dosed animals. Statistically significant decreases in mean daily food consumption (M:15000; F: 10000, 15000 ppm). Dose related decreased feed efficiency was seen in males (2000, 10000, 15000 ppm) and females (10000, 15000 ppm). Minimal to mild decreases in group mean RBC, hemoglobin and hematocrits was observed (M & F: 2000, 10000, 15000) and considered biologically significant. Also accompaning these erythrocytic changes were increased corpuscular volume and reticulocyte counts with decreased mean corpuscular hemoglobin concentrations. A mild leucocytosis was noted in males (10000, 15000 ppm). Mean relative liver weights were slightly elevated in females (2000 ppm) and significantly increased in males (15000 ppm) and females (10000, 15000 ppm). Other increased relative organ weights were attributed to inanition. Pigment accumulation in kidney proximal tubules was observed (M & F: 10000, 15000 ppm). Slight splenic hematopoiesis was observed (M:10000, 15000 and F:2000 ppm and above). NOEL (M/F)=100 ppm (based on decreased body weight, body weight gain, feed efficiency, increased relative mean liver weight and mild hemolysis) **Acceptable** (Miller, 9/26/96)

Dog Subchronic Dietary Toxicity Study

51974-029; 119838; "A Subchronic (3-month) Toxicity Study of DPX-66037-24 in the Dog Via Dietary Administration" (Author: J.E. Atkinson; Bio/dynamics, Inc., East Millstone, NJ, Project No. 91-3653, 12/20/91); DPX-66037-24(95.6% triflusulfuron-methyl); 0, 100, 4,000 and 8,000 ppm (averaged intake (M) 3.9, 146.1, 267.6 and (F) 3.7, 159.9 and 250.7 mg/kg/day) in diets; 4 Beagle dogs/sex/dose; observations- two high dose females were sacrificed in extremis showing marked body weight loss with low food consumption and frank anemia, other high dose animals exhibited little to no weight gain with food consumption slightly decreased in the early weeks of the study; decreased erythrocyte count and associated hematocrit and hemoglobin levels were noted at 1 1/2 and 3 months with a compensatory elevated reticulocyte count; hepatotoxcity was demonstrated by elevated levels of serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase and elevated liver weights and microscopic evidence of bile stasis in the 4,000 and 8,000 ppm groups; in mid and high dose males testicular atrophy and decreased testicular weights were characterized by aspermatogenesis, decreased seminiferous tubule thickness and germinal epithelial cytoplasmic vacuolation; sternal and femoral bone marrow hypercellularity was seen in high dose animals; NOEL(M/F)= 100 ppm (based on microscopic findings in the liver and testes); **Possible Adverse Effect**: testicular atrophy, aspermatogenesis; **Acceptable**. (Miller, 9/17/93)

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

51974-093; 147897; Subacute Dermal Toxicity; 822; Rabbit; "Repeated Dose Dermal Toxicity: 21-Day Study with DPX-66037-24 (Triflusulfuron Methyl) in Rabbits"; S.A. MacKenzie; E.I. du Pont de Nemours and Co., Haskell Lab. for Tox. and Ind. Med., Newark, DE; Laboratory Report No. HRL 552-93; 9/27/93 ; Triflusulfuron Methyl (DPX-66037-24, 95.6% purity); 0, 50, 300, 1000 mg/kg applied dermally 6 hrs/day for 21 days ; 822; 5 New Zealand White rabbits/sex/dose; observations- There were no test article related mortalities or clinical signs of systemic toxicity. Slight or mild erythema was observed in animals of all groups (including controls). Mild skin

trauma was noted in a few animals but was not considered compound-related. Microscopic skin lesions observed in both treated and control groups included, minimal to mild inflamation and acanthosis. Lesions were attributed to testing procedure. Statistically significant differences in mean body weight gain were observed over a few intervals in female rabbits but did not exibit a dose-response and were not considered compound related. No other compound related changes were noted any other parameter including body weight or body weight gain, food consumption, hematology or clinical chemistry analysis. Systemic and Dermal NOEL(M/F)= NOAEL(M/F)=1000 mg/kg b.w. (based on no effects at HDT); **Acceptable** (Miller, 7/16/96)